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(57) Abstract

The invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical aqueous gel formulations containing 9-(2-hydroxyethoxymethyl)guanine, otherwise known as aciclovir, that exhibit the required stability and allow flux of the compound into the skin.

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MEDICAMENTS CONTAINING ACYCLOVIR

This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing 9-(2-hydroxyethoxymethyl)guanine, otherwise known as aciclovir, and hereinafter referred to as such.

Aciclovir and pharmaceutically acceptable salts and esters thereof are known to have antiviral activity against various classes of DNA and RNA viruses both *in vitro* and *in vivo*, see UK patent No. 1 523 865. In particular the compound is active against herpes simplex virus which causes herpetic keratitis in rabbits, herpetic encephalitis in mice, and cutaneous herpes in guinea pigs. Aciclovir has been found to be effective in the treatment of herpes simplex virus and herpes zoster virus in humans. Hereafter, references to aciclovir should be understood to include also its pharmaceutically acceptable salts and esters unless the context clearly indicates otherwise.

Aciclovir suffers from the disadvantage that it has a low solubility in water and is almost totally insoluble in hydrophobic solvent systems. It is accordingly difficult to produce a topical formulation containing a sufficient dissolved concentration of active ingredient for it to exert its full effect and also to optimise the flux of the compound into the skin. In addition to ease of release, it is also important that any formulation of a pharmaceutically active compound should be stable for long periods of time, should not lose its potency, should not discolour or form insoluble substances or complexes, and also should not be unduly irritating to the skin or mucosa.

European Patent No. 0 044 543 describes oil-in-water topical pharmaceutical formulations of aciclovir wherein the aqueous phase contains at least 30% of a water miscible polyhydric alcohol,

Co-pending International patent application No. PCT/GB97/00779 relates to oil-in-water topical pharmaceutical formulations of aciclovir comprising at least 10% by weight of diethylene glycol monoethyl ether.

Surprisingly, it has now been found that, despite its poor solubility in water, it is possible to formulate aciclovir into a topical aqueous gel formulation that exhibits the required stability and allows flux of the compound into the skin.

Accordingly, in a first aspect, the present invention provides an aqueous gel formulation for the topical delivery of aciclovir, the formulation comprising

(a) aciclovir, or a pharmaceutically acceptable salt or ester thereof, preferably in powder form;
(b) a pharmaceutically acceptable thickening or gel forming agent;
(c) a pharmaceutically acceptable co-solvent;
(d) purified water

Such a topical formulation may contain from 0.075% to 10% w/w aciclovir or a pharmaceutically acceptable salt or ester thereof, relative to the total weight of the formulation, from 0.5% to 80% w/w of pharmaceutically acceptable co-solvent, from 15% to 80% w/w water and a pharmaceutically acceptable gel forming agent or thickener. Compositions according to the invention may also include one or more buffering agents and optionally a surfactant. All ingredients will be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Such formulations have particularly advantageous properties, in particular, enhanced efficacy together with low irritancy and good physical stability.

Preferred compositions contain 1-10% by wt of aciclovir, 1-65% by wt of co-solvent, 0.01-5% of a buffering agent, 0.001-8% of a surfactant and up to 15% of an organic or inorganic polymeric or colloidal gel thickener, with purified water to 100%.

Preferably formulations according to the invention contain at least 15% water.

Suitable thickening or gel forming agents include colloidal silicon dioxide, HPMC (hydroxypropylmethylcellulose) and carbomer 943P.

Suitable co-solvents include glycerol formal, propylene glycol, dimethyl isosorbide (DMI), NDMS (n-decylmethylsulphoxide), isopropyl alcohol and diethylene glycol monoethyl ether.

Diethylene glycol monoethyl ether is manufactured by Gatttefossé S.A., 36 Chemin de Genas, b.p. 603, 69804 Saint-Priest Cedex, France, under the tradename TRANSCUTOL™.

Suitable buffering agents include triethanolamine (TEA), sodium hydroxide, potassium citrate, sodium citrate, sodium phosphate and EDTA (ethylenediaminetetra-acetic acid).

Suitable surfactants include anionic surfactants such as sodium lauryl sulphate, cationic surfactants such as benzalkonium chloride and, preferably, non-ionic surfactants such as polyvinyl alcohol and polyoxyethylene sorbitan fatty acid esters (polysorbates). Particularly preferred is Tween 20® (polysorbate 20).

In particularly preferred embodiments, the composition comprises from 2 to 6% w/w aciclovir, e.g. 5%, from 20 to 50% w/w co-solvent, e.g. 40%, together with water, a pharmaceutically acceptable thickener and a buffering agent.

In a second aspect, the present invention provides the use of an aqueous gel formulation of the invention in the treatment or prevention of viral infections caused by a virus of the Herpes family, for example by Herpes zoster, Herpes varicella or Herpes simplex type I or 2. Also provided is the use of aciclovir in the preparation of an aqueous gel formulation for the treatment or prophylaxis of infectious disease caused by a member of the Herpes family of viruses, particularly Herpes simplex, Herpes varicella or Herpes zoster.

Aciclovir may be prepared by methods known in the art, for example, as disclosed in British patent No. GB1523865, the content of which is hereby incorporated herein by reference. It will be appreciated that salts of aciclovir can be prepared and, accordingly, the present invention extends to formulations comprising physiologically acceptable salts of aciclovir. The particle size of the

crystalline material may be reduced by conventional methods, for example, by micronisation.

Gel formulations according to the invention in which the thickener is Carbomer 943P may have the following composition:

Ingredient	% w/w
aciclovir	2-6%
propylene glycol	0-65%
Transcutol ™	0-50%
EDTA	0-1%
carbomer 943P	0.1-5%
triethanolamine	0-1%
Tween 20®	0-5%
Glycerol Formal	0-65%
NDMS	0-2%
water	to 100%

Gel formulations according to the invention in which the thickener is colloidal silicon dioxide may have the following composition:

Ingredient	% w/w
aciclovir	2-6%
propylene glycol	0-65%
Transcutol ™	1-65%
colloidal silicon dioxide	3-15%
TEA or EDTA buffer	0-1%
Tween 20®	0.5-5%
water	to 100%

Formulations according to the invention may be buffered to improve stability. The compositions may be buffered to have a pH of from about 4 to about 13. Suitable buffers are those discussed above which are physiologically acceptable upon topical administration. Preferred high pH formulations have a pH above 9, suitably in the range 9 to 11. The preferred buffer for high pH formulations is

sodium hydroxide. Low pH formulations may be buffered to have a pH of from about 4 to about 9. Preferred low pH formulations have a pH of between 4 and 8, suitably below 7, desirably in the range 4 to 6. The preferred buffer for low pH formulations is triethanolamine (TEA) or a mixture thereof with EDTA.

High pH gel formulations according to the invention may have the following composition:

Ingredient	% w/w
aciclovir	2-6%
HPMC	0.75-3%
sodium hydroxide	0.1-2%
IPA (isopropyl alcohol)	0-4%
ethanol	0-4%
propylene glycol	1-10%
Transcutol ™	0-50%
water	to 100%

The formulations of the invention may, if desired, include one or more pharmaceutically acceptable preservatives or other excipients well known in the field of topical pharmaceuticals e.g. humectants, emollients, antioxidants, chelating agents etc. Optionally, the formulations may include ingredients well known from the cosmetics field such as colourants or fragrances.

Preservatives which may optionally be employed in formulations according to the present invention include thiomerosal, benzalkonium chloride, methyl paraben.

Humectants which may optionally be employed in formulations according to the present invention include propylene glycol, glycerol, sorbitol.

Emollients which may optionally be employed in formulations according to the present invention include cetostearyl alcohol, glycerin, glyceryl monostearate.

Antioxidants which may optionally be employed in formulations according to the present invention include butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), ascorbic acid.

Chelating agents which may optionally be employed in formulations according to the present invention include citric acid monohydrate, EDTA.

It will be appreciated by those skilled in the art that the formulations according to the invention may, if desired, contain a combination of two or more active ingredients. Accordingly, the present invention further provides topical formulations in accordance with the invention which contain aciclovir and at least one other active ingredient. Suitable active ingredients for use in such combination formulations include acemannan, pain relief or anaesthetic agents such as lidocaine or bupivocaine and antipruritic agents such as menthol.

The present invention also provides a method for the preparation of a topical pharmaceutical formulation, as hereinbefore defined, which comprises mixing the aciclovir, co-solvent and pharmaceutically acceptable thickener with water.

The manner of formulating the gel composition will of course vary according to the amount and nature of the constituents, but nevertheless follows known techniques in emulsion technology (see the Pharmaceutical Codex, London, the Pharmaceutical Press, 1979). For example, the aciclovir may initially be mixed with water to form a "drug phase" in which the drug may be in solution or a mixed solution/suspension, and this may then be incorporated into a "gel phase". The gel phase may be formed by slow addition of the thickener, with propeller agitation, to a mixture of water, co-solvent and any necessary buffering agent. Alternatively, the aciclovir may be mixed with the co-solvent, buffering agent (if used) and water and then the thickener or gelling agent added slowly, with propeller agitation. Any additional optional ingredients may be added at the end, mixing slowly to avoid entrapment of air into the gel, or before addition of the thickener, as appropriate. Any additional active ingredient may be added with the aciclovir to the drug phase.

A topical formulation of the present invention may be used in the treatment or prevention of viral infections caused for example by Herpes zoster, Herpes varicella and Herpes simplex types I and 2, which cause diseases such as shingles, chicken pox, cold sores and genital herpes. Administration of medicament may be indicated for the treatment of mild, moderate or severe symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered and the frequency of administration will depend on many factors and may ultimately be at the discretion of an attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. The formulation may desirably be applied to the affected area of skin from 1 to 6 times daily, preferably from 3 to 5 times. A further aspect of the present invention therefore provides a method of treating a herpes viral infection in a mammal, particularly a human, by topical administration of a formulation according to the invention.

The chemical and physical stability of the formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay after prolonged storage of the product. Physical stability may be determined after storage or stress e.g. centrifugation by microscopic examination or by visual appearance (e.g. looking for separation, settling or other physical changes).

The following examples illustrate the invention and are not intended as limitations thereof.

Example 1

Ingredient	% w/w
aciclovir	5%
propylene glycol	12%
Transcutol TM	40%
colloidal silicon dioxide	10%
TEA/EDTA buffer in water	to 100%

Procedure: Weigh all materials except colloidal silicon dioxide into suitable container. Mix with propeller agitation. Slowly add colloidal silicon dioxide until uniformly mixed.

Example 2

Ingredient	% w/w
aciclovir	5.0%
propylene glycol	10%
Transcutol ™	40%
EDTA Powder	0.05%
carbomer 943P	0.75%
triethanolamine	0.60%
water	to 100%

Procedure: Mix water and aciclovir by stirring with propeller agitation, to form drug phase. Dissolve EDTA in water, propylene glycol, and Transcutol. Slowly sprinkle in carbomer 934P while mixing with propeller agitation. Mix until carbomer is completely dispersed. Add "drug phase" and mix well using sweep agitation. Add triethanolamine, mixing gently with sweep agitation so as not to entrap air into bulk.

Examples 3-7

The formulations of examples 3-5 below were made according to the procedure set out in example 2 above. The formulation of example 6 was made according to the procedure set out in example 1 above. The formulation of example 7 was made by mixing water and aciclovir by stirring with propeller agitation to form the "drug phase". Sodium hydroxide was dissolved in water, ethanol, propylene glycol and Transcutol and HPMC was slowly sprinkled in, while mixing with propeller agitation. Mixing continued until the HPMC was completely dispersed, then the "drug phase" was added and mixed well using sweep agitation.

Ingredient (w/w%)	Example No.				
	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
aciclovir	5.00	5.00	5.00	5.00	2.64
Carbomer 934P	0.75	0.75	0.75	0.75	
EDTA powder	0.05	0.05	0.05	0.05	
propylene glycol	65.00	65.00	5.00		3.50
Tween® 20		3.00			
glyceryl formal			60.00		
colloidal SiO_2				6.00	
Transcutol®				50.00	40.00
Triethanolamine (99%)	0.60	0.60	0.60		
HPMC					1.66
sodium hydroxide					0.80
ethanol					2.00
water (USP)	to: 100%	to: 100%	to: 100%	to: 100%	to: 100%

Example Formulations 3-6 Experimental Data

1) Herpes Simplex Virus Animal Data: Mouse Snout Model

1.i) METHODS: Female HRS/J mice were infected cutaneously with wild-type HSV-1. After the mice were anaesthetised the skin of the snout region was lightly abraded with a roto-tool. Groups of ten mice were then innoculated on the skin of the snout from an SC-16 HSV stock solution diluted to a final concentration of 1.1 E8 PFU/ml. The abrasion area was then swabbed for ten seconds with a sterile cotton swab soaked with the viral stock.

1.ii) TREATMENT: Mice were treated for four days starting three days post-innoculation (PI) and continuing through day seven. Mice in four groups of 10 were treated topically twice daily with one of the formulations from Examples 3-6. A further group of 10 mice

received no treatment (negative control) and one group of 10 were treated with aciclovir oil-in-water cream (positive control) as disclosed in EP-B-0044543.

1.iii) ASSESSMENT: Lesions were scored at the same time each day. The scoring system is outlined below:

0 = Normal skin
+1 = 1 to 5 discrete lesions
+2 = $\geq$ 6 discrete lesions
+3 = confluent lesions
+4 = necrotic or ulcerative lesions or death

1.iv) STATISTICAL ANALYSIS: The lesions are graphed and the average area under the curve (AUC) for days 5 through 7 is calculated to compare formulation efficacies.

Formulation	% reduction in AUC compared to no treatment	% Survival
aciclovir cream	81.6	70
Ex.3	86.9	100
Ex.4	81.6	100
Ex.5	80.2	90
Ex.6	82.6	70
No treatment	0.0	0

2) Guinea Pig Cutaneous Model of Herpes Infection

2.i) Infection procedure

The left hand flanks of female guinea-pigs weighing in excess of 600g (Dunkin/Hartley strain, supplied by Interfauna, UK.) were closely shaved and the remaining fur removed with Nair® depilatory cream. After approximately four hours the animals were sedated and their exposed flanks infected with the H31

strain of HSV-1. Infection was by multi-inoculation through a 20µl drop of virus suspension (containing $3x10^5$ pfu of virus) at six sites using a disposable multipuncture apparatus with 6 x 2mm tines. (Bignell Surgical Instruments Ltd., Littlehampton, West Sussex, UK.)

After infection, the animals were randomly divided into groups of 2, to include untreated virus control and 6 treatment groups.

2.ii) Treatment regimen

Treatment of infected animals with test formulations commenced 18 hours post infection and continued twice daily (8.30 a.m. and 4.30 p.m.) for 3 days. Therapy consisted of 1ml of test cream being applied directly to the infected flank from previously loaded 5ml syringes. Four groups of animals were treated topically twice daily with one of the formulations from Examples 3-7. A further group of 2 guinea pigs received no treatment (negative control) and one group was treated with aciclovir oil-in-water cream (positive control) as disclosed in EP-B-0044543.

2.iii) Method of assessment

Daily visual assessment of infection began prior to the application of the first dose of treatment and continued for five days. The final assessment was made three days after the final treatment was given. The scoring was based on the following system:-

score	comment
0.0	no signs of visible infection.
0.5	very early papules (not raised) slight erythema.
1.0	papules and erythema.
2.0	0-5 pustules and erythema.
3.0	6+ pustules and erythema.
4.0	coalescence of pustules.
5.0	crusting/ scabbing of pustules.

In untreated animals, very early papules (0.5) are usually apparent by day 1 post infection and after 2 to 4 days have progressed to pustules with a score of between 1.0 and 3.0. Coalescence of pustules (4.0) occurs around day 5 post infection and by day 7 crusting and scabbing have commenced.

The daily scores for each flank were totalled and the average score per flank per day calculated.

2.iv) Results: Average lesion score per flank

Example	Day 1	Day 2	Day 3	Day 4	Day 7
Untreated	3.0	12.5	22.5	24.5	28.0
aciclovir cream	3.0	8.5	6.0	7.5	15.0
3	3.0	6.0	16.5	17.5	25.5
4	3.0	6.0	6.5	15.5	20.5
5	3.0	6.0	16.5	18.0	25.5
6	3.0	8.5	17.5	21.0	30.0
7	2.8	5.8	5.5	7.0	5.5

Discussion

In the mouse study, the formulations of the present invention are shown to be comparable to aciclovir cream in the levels of reduction in lesion scores, and % survival of the animals. In the guinea pig study, all the tested formulations of the invention showed an antiviral effect during the three days of treatment (lesion scores compared to untreated control) and Examples 4 and 7 were comparable to aciclovir cream during treatment, although the Example 4 formulation exhibited a "bounce back" effect on cessation of treatment.

These results demonstrate that the formulations of the invention provide aciclovir in topical aqueous gel formulations that allow flux of the compound into the skin, despite its poor solubility in water, to give an antiviral effect upon topical application.

Claims

1. An aqueous gel formulation for the topical delivery of aciclovir, the formulation comprising

   (a) aciclovir, or a pharmaceutically acceptable salt or ester thereof;
   (b) a pharmaceutically acceptable thickening or gel forming agent;
   (c) a pharmaceutically acceptable co-solvent;
   (d) purified water

2. An aqueous gel formulation according to claim 1 comprising 1-10% by wt of aciclovir, 1-65% by wt of co-solvent, 0.01-5% of a buffering agent, 0.001-8% of a surfactant and up to 15% of an organic or inorganic polymeric or colloidal gel thickener.

3. An aqueous gel formulation according to claim 1 or claim 2, comprising at least 15% water.

4. An aqueous gel formulation according to any preceding claim wherein the thickening or gel forming agent is selected from the group consisting of colloidal silicon dioxide, HPMC (hydroxypropylmethylcellulose) and carbomer 943P.

5. An aqueous gel formulation according to any preceding claim wherein the co-solvent is selected from the group consisting of glycerol formal, propylene glycol, dimethyl isosorbide (DMI), isopropyl alcohol and diethylene glycol monoethyl ether.

6. An aqueous gel formulation according to any preceding claim having a pH of from about 4 to about 13.

7. An aqueous gel formulation according to claim 6 having a pH of above 9,

8. An aqueous gel formulation according to claim 7 having a pH in the range 9 to 11.

9. An aqueous gel formulation according to any preceding claim consisting essentially of 2.64% w/w aciclovir, 3.50% w/w propylene glycol, 1.66% w/w hydroxypropylmethylcellulose, 0.80% w/w sodium hydroxide, 40.00% w/w Transcutol®, 2.00% w/w ethanol and 49.40% w/w purified water.

10. An aqueous gel formulation according to any preceding claim consisting essentially of 5.00% w/w aciclovir, 65.00% w/w propylene glycol, 0.75% w/w Carbomer 934P, 0.05% w/w EDTA powder, 3.00% w/w Tween® 20, 0.60% w/w triethanolamine and 25.60% w/w purified water.

11. Use of an aqueous gel formulation according to any one of claims 1 to 10 in the treatment or prevention of viral infections caused by a virus of the herpes family.

12. Use according to claim 11 wherein the infection is caused by herpes zoster, herpes varicella or herpes simplex virus type I or 2.

13. Use of aciclovir, a pharmaceutically acceptable thickening or gel forming agent and a pharmaceutically acceptable co-solvent in the preparation of an aqueous gel formulation for the treatment or prophylaxis of infectious disease caused by a member of the herpes family of viruses, particularly herpes simplex, herpes varicella or herpes zoster.

14. A method for the preparation of a topical pharmaceutical formulation according to any one of claims 1 to 10 which comprises mixing aciclovir, a co-solvent and a pharmaceutically acceptable thickener with water.

15. A method of treating a herpes viral infection in a mammal, particularly a human, by topical administration of a formulation according to any one of claims 1 to 10.